REMARKS

This is in response to the Advisory Action mailed April 1, 2008 and the arguments set forth in the Office Action mailed September 19, 2007.

Independent claim 1 and its dependent claims 2-18 are pending in this application. Claims 8-10, 12-13, and 15-18 are currently amended. Claim 8 has been amended such that it is now a method claim depending from claim 1. Support for this amendment can be found throughout the originally filed application, e.g., at paragraph 0052. Claims 9-10 and 15-18, which depend from claim 8, have been amended so as to be consistent with the amendment to claim 8. Claims 12-13 have been amended to fix typographical errors. No new matter is introduced. Entry of these amendments is respectfully requested.

Claim Rejections – 35 U.S.C. § 103(a)

In the Office Action of September 19, 2007, the Examiner rejected claims 1-7 and 11-14 under 35 U.S.C. § 103(a) as being unpatentable over Metz et al. (AJH 1:58-60 1988). The Examiner asserted that, though Metz requires sodium as well as calcium, "applicants do not exclude sodium." As set forth in the Amendment and Response filed February 13, 2008, Applicants disagree because Metz does not disclose, teach or suggest a benefit attributable to calcium, as recited in the current claims. Instead, Metz' hypothesis and results suggest that the induction of weight loss is attributable to the simultaneous administration of calcium and sodium. (See, e.g., p. 59 ("there was an inverse relationship between dietary Ca^{2+} and Na^{+} and body weight.")) Indeed, because both calcium and sodium were varied simultaneously (See Table 1, p. 59), Metz offers no basis for a person of skill in the art to infer anything about the effect of calcium alone on body weight.

In the Advisory Action mailed April 1, 2008, the Examiner asserts that Metz discloses a benefit attributable to calcium, and refers to several excerpts from Metz to support this contention. Applicants disagree because the statements, when considered in context and not in isolation, do not disclose or suggest a benefit attributable to calcium. Two statements merely describe calcium's effects on metabolism, without any suggestion as to whether the effect leads to a weight-related benefit, or detriment, or neither. For two statements, consideration of the data reported and/or supporting authority cited in Metz actually demonstrates that Metz teaches away from a weight-related benefit attributable to calcium. And in light of the fact that calcium

and sodium were varied simultaneously in Metz, any suggestion that Metz demonstrates a weight-related benefit attributable to calcium is unfounded.

The Examiner asserts that the statement "calcium's known effects on lipid metabolism" in Metz (Abstract) teaches a benefit attributable to calcium. Applicants disagree because this statement does not suggest whether the effect leads to a weight-related benefit, or a detriment, or neither. It merely states that calcium has an effect on lipid metabolism. Any assertion that the calcium's disclosed effect on lipid metabolism leads to a weight-related benefit is unfounded, and suggests that the Examiner is employing impermissible hindsight based on Applicants' later work.

The Examiner also asserts that statement "lower body weights in Ca^{2+}-supplemented animals" in Metz (p. 58) suggests a weight-related benefit attributable to calcium. Applicants disagree with the Examiner's interpretation of this statement as reflecting a weight-related benefit attributable to calcium. The authority cited by Metz for this point actually teaches away from this conclusion, because the reported data undermines the existence of a correlation between calcium intake and a weight-related benefit, because animals receiving a lesser amount of calcium appear to have lost the most weight.

As authority for the above-quoted statement, Metz cites an abstract entitled "Effects of Ca^{2+} and Na^{+} on Blood Pressure, Food Consumption and Weight in the Spontaneously Hypertensive Rat," published in Kidney International, Vol. 27, 1985 (p. 193), submitted herewith for the Examiner's reference as Exhibit 1. The abstract reports results of experiments in which the sodium and calcium content were varied in rats' diets in order to determine the effects of calcium and sodium on blood pressure, food consumption and weight. Some rats were fed ad libitum. The abstract reports that "[t]he [high] Ca^{2+} /[high] Na^{+} group consumed the greatest amount of food, while the [high] Ca^{2+} /[normal] Na^{+} consumed the least," and that "[t]he high Ca^{2+} /[normal] Na^{+} had the lowest [blood pressure] and body [weight], despite receiving a smaller dose of Ca^{2+} and Na^{+} overall." Thus, the weight-related benefit was observed in the group that received a lesser amount of calcium, which undermines any assertion of a correlation between calcium intake and a weight-related benefit. Accordingly, rather than disclose or suggest a weight-related benefit attributable to calcium, the abstract teaches away from this conclusion. The Examiner's assertion that the statement "calcium's known effects on lipid metabolism" discloses or suggests such a weight-related benefit is in conflict with the data.

The Examiner also asserts that the statement in Metz that "dietary calcium is affecting cell lipid metabolism or possibly the cation is influencing thermogenesis and caloric utilization" (p. 60) suggests a weight related benefit attributable to calcium. Applicants disagree because this statement does not suggest whether calcium leads to a weight related benefit, or detriment, or neither. It merely notes that calcium has an effect on lipid metabolism, thermogenesis and/or caloric utilization. The assertion by the Examiner that it reflects a weight-related benefit attributable to calcium suggests, as noted above, that the Examiner is employing impermissible hindsight based on Applicants' own work.

Furthermore, the entire Metz study – the hypothesis, materials, methods, results and discussion – involve the simultaneous manipulation of calcium and sodium. The statement that "dietary calcium is affecting cell lipid metabolism or possibly the cation is influencing thermogenesis and caloric utilization," referenced by the Examiner, is made in the course of the authors' discussion of the results of the investigation. Because both calcium and sodium were varied simultaneously in the experiments reported in Metz, the authors would have no basis for ascribing any effect to calcium alone. Accordingly, Metz cannot be used to support the suggestion that any benefit, including a weight-related benefit, is attributable to calcium alone. Any suggestion to the contrary is unfounded.

Finally, read in context, the statement undermines any suggestion of a weight-related benefit attributable to calcium. The experiments reported in Metz were performed on two strains of rats, spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats (WKY) (Abstract). Both rat strains were administered the same calcium / sodium dosing regimen. (p. 58, right-hand column, first paragraph.) However, one of the two rat strains did not exhibit a decreased body fat content on the high calcium / high sodium diet as compared to those on the normal calcium / normal sodium diet. (p. 60, left column, first full paragraph, last sentence.) The statement excerpted by the Examiner is made by the investigators in an attempt explain this observed inconsistency between the two rat strains. The authors speculate that "[t]he difference in the strains' responses suggest that the mechanisms involved are far more complex than simply an effect of Ca^{2+} on fat absorption. It appears more likely that dietary calcium is affecting cell lipid metabolism or possibly the cation is influencing thermogenesis and caloric utilization." (p. 60, left column, final full paragraph (emphasis added).) Thus, the authors are attempting to provide an explanation for this observed inconsistency, and they guess that calcium may have

contributed. And their guess is without any experimental basis, because, as noted above, their experiments varied sodium and calcium simultaneously, thus undermining their ability to draw any conclusions about the effect of calcium alone. Accordingly, the statement in Metz that "dietary calcium is affecting cell lipid metabolism or possibly the cation is influencing thermogenesis and caloric utilization" does not, and cannot, disclose or suggest any weight-related benefit attributable to calcium.

Accordingly, contrary to the Examiner's assertions, the quoted passages in Metz do not disclose or suggest a weight-related benefit attributable to calcium, because two statements merely describe calcium's effects on metabolism, without any suggestion as to whether the effect leads to a weight-related benefit, or detriment, or neither, and for two statements, consideration of the data and/or supporting authority actually undermines the conclusion that calcium leads to a weight-related benefit. Furthermore, in light of the fact that calcium and sodium were varied simultaneously in Metz, any suggestion that Metz demonstrates a weight-related benefit attributable to calcium is unfounded. Any assertions to the contrary suggest that the Examiner is employing impermissible hindsight based on Applicants' own work.

Metz does not teach inducing a weight benefit attributable to calcium, and therefore the claims are allowable over Metz. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Claim Rejections – 35 U.S.C. § 102(b)

The Examiner has rejected claims 8-10 and 16-18 under 35 U.S.C. § 102(b) as being unpatentable over Schroeder et al. (U.S. Patent No. 4,027,043). Applicants traverse because Schroeder fails to disclose, either expressly or inherently, every element of the claims.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. In order to anticipate, the elements of the prior art must be present and arranged as required by the claim. MPEP § 2131.

Schroeder fails to disclose each and every element of claims 8-10 and 16-18. These claims now depend from claim 1, which recites "a method of regulating weight in an overweight non-human animal comprising in combination, during a period of time (a) administering on a daily basis one or more servings of calcium-containing dairy products to the animal in an amount sufficient to induce weight loss, reduce weight gain, and/or increase the metabolic consumption

of adipose tissue in the non-human animal, the one or more servings comprising a therapeutically effective amount of calcium above suboptimal levels, wherein the dairy product comprises at least about 0.4% calcium, and (b) maintaining the overweight animal on a restricted caloric diet below ad lib." Schroeder fails to disclose all elements of the claims for at least the following reason.

Schroeder does not disclose "maintaining the overweight animal on a restricted caloric diet below ad lib." Instead, Schroeder discloses an animal feed supplement which is "sufficiently palatable to permit free choice feeding" and which supplies the energy requirements needed for "maintenance and weight gain" (Abstract). Thus, Schroeder does not anticipate claims 8-10 and 16-18, all of which depend from claim 1 and include all of its elements, and claims 87-10 and 16-18 are allowable over Schroeder.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. Accordingly, Applicants request that the Examiner issue a Notice of Allowance indicating the allowability of claims 1-18 and that the application be passed to issue. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is hereby invited to telephone the undersigned at the number provided.

In view of the above amendments and remarks, Applicants believe the pending application is in condition for allowance.

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Respectfully submitted,

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Exhibit 1

SN 10/827301

EFFECTS OF CAPTOPRIL ON RENAL HEMODYNAMICS AND HIPPURAN EXCRETION IN RENOVASCULAR HYPERTENSION (RVH). A.K. Hoola,* C.E. Kaufman, V. Ficken,* C. Ryals,* W. Allen,* J.C. Leonard.* Dept. of Med. and Radiol. Univ. of Oklahoma and VAMC, Oklahoma City, OK.

Captopril (Cp) may cause acute renal failure in patients (pts) with bilateral renal artery stenosis (RAS) but the hemodynamic effects of Cp in unilateral RAS are undefined. Eighteen hypertensive pts undergoing arteriography and Cp stimulated renal vein renins (SRVR) were divided into 3 groups Group I (6 pts) had >75% RAS, lateralizing SRVR, and a good response to surgery (5/5). Group II (5 pts) has RAS but nonlateralizing SRVR. Group III (7 pts) had no RAS. Single kidney glomerular filtration rate (SKGFR) and effective renal plasma flow (SKERPF) were measured by radionuclide methods before and 1 hour after 25 mg. of Cp. The SKGFR fell >10% in all kidneys with RAS in Group I (mean pre/post = 45.5/33.3cc/min; p<.01); but showed no consistent changes in the contralateral kidneys or in Groups II or III. Blood pressure fell similarly in the 3 groups. The table presents mean values expressed as a % change from baseline.

	Group I	Group II	Group III
Δ SKGFR%	-30.1±6**	23.4±12	17.8± 9
Δ SKERPF%	-32.5±11*	15.6±16	5.0 ± 6

*= p<.025; **= p<.01

The baseline hippuran excretion curve, abnormal in 3/11 stenotic kidneys (Group I + II) showed delayed excretion in 9/11 kidneys, including all of Group I, after Cp (p<.05).

In conclusion, Cp reduces both renal perfusion and GFR and delays hippuran excretion in kidneys with functionally significant RAS. It also impairs hippuran excretion in the presence of RAS which is otherwise of no apparent significance.

IDENTIFICATION OF THREE NAK-ATPASE INHIBITORS IN HUMAN PLASMA. R.A. Kelly,* D.S. O'Hara,* W.E. Mitch, T.W. Smith.* Harvard Med. Sch., Boston, MA.

Endogenous NaK-ATPase (NKA) inhibitors have generated intense interest because they might play an important role in the regulation of blood pressure and sodium homeostasis. Indeed, we have shown that NKA inhibitory activity is higher in desalted plasma from hypertensive patients than from normotensive controls ($12.5\pm1.8 \times 10^{-10}$M, n=12, vs $2.9\pm2.5 \times 10^{-10}$M, n=6, ouabain equivalents; mean ±SE; p<0.02). Using reverse-phase HPLC, we have identified three fractions (EI_1, EI_2 and EI_3) in desalted, deproteinized plasma from normal human subjects that inhibit NKA activity and displace ^{3}H-ouabain from the enzyme. They also crossreact with digoxin-specific polyclonal antibodies, implying a structural similarity with digitalis. In addition, we found one other fraction (IR_1) that shows crossreactivity with polyclonal and monoclonal digoxin-specific antibodies, but does not inhibit NKA. All fractions have a molecular weight <2,000 and are resistant to acid hydrolysis and protease digestion. To determine if binding of EI_1, EI_2 and EI_3 to NKA resembles that of digitalis, we examined whether increasing concentrations of KCl or the absence of ATP in the incubation media would lower the affinity of each fraction for the enzyme. Only the EI_3 peak shows a reduced affinity for NKA in the presence of KCl; unlike ouabain, none of the inhibitory fractions requires ATP for binding. Thus, desalted, deproteinized plasma contains at least three factors which may be physiologically important inhibitors of NKA, exhibiting some characteristics of the digitalis glycosides.

EFFECTS OF CA^{2+} AND NA^+ ON BLOOD PRESSURE, FOOD CONSUMPTION AND WEIGHT IN THE SPONTANEOUSLY HYPERTENSIVE RAT. N. Karanja,* J. Metz,* D. Lee,* T. Phanouvong,* D. McCarron. Oregon Health Sciences University, Portland, OR.

The spontaneously hypertensive rat (SHR) exhibits abnormal Ca^{2+} metabolism. Previous studies have shown a protective effect of Ca^{2+} and Na^+ on the expression of hypertension in the SHR. We assessed systolic blood pressure (BP), food consumption and weight (wt) in the SHR on varying Ca^{2+} and Na^+ diets.

75 SHRs were assigned to 1 of 5 diets at 6 wks of age (WOA): high Ca^{2+} (2%)/high Na^+ (1%); high Ca^{2+}/normal (N) Na^+ (.45%); control 1% Ca^{2+}/.45% Na^+; low Ca^{2+} (.1%)/NNa^+; low Ca^{2+}/low Na^+ (.25%). With 15 animals per diet, 5 were assigned to a pair fed, weight fed or ad libitum feeding regimen. Weight and BP were measured every 2 wks from 10 WOA. Food was administered daily. ANOVA and multiple range testing were used. Mean (±SD) BP (mmHg) by diet at 16 WOA:

HCa/HNa	HCa/NNa	NCa/NNa	LCa/NNa	LCa/LNa
197±15	179±21	202±22	204±23	224±18

No differences were noted in BP or wt between feeding methods. BPs in the HCa^{2+} diets were lower (p<.01) than in the LCa^{2+}/LNa^+ diet. The HCa^{2+}/HNa^+ group consumed the greatest amount of food, while the HCa^{2+}/NNa^+ consumed the least (p<.05). The high Ca^{2+}/NNa^+ had the lowest BP and body wt, despite receiving a smaller dose of Ca^{2+} and Na^+ overall. We conclude that: 1) HCa^{2+} diets result in lower BP, 2) Ca^{2+}'s BP effect may be maximized by a NNa^+ diet, and 3) These effects of Ca^{2+}/Na^+ are independent of feeding method.

ANTIHYTERTENSIVE DRUGS AND SODIUM RESTRICTION - ANALYSIS OF THEIR INTERACTION BASED ON THE RENAL FUNCTION CURVE. G.Kimura, F.Deguchi, S.Kojima, M.Yokouchi, T.Ashida, M.Kuramochi, K.Ito and M.Ikeda. Natl. Cardiovascular Ctr., Osaka, Japan.

The hypotensive effects of some drugs are augmented under sodium restriction, while those of others are not. The mechanisms of these interactions were theoretically analyzed based on the renal function(arterial pressure-natriuresis)curve.

Four-week studies were performed in 24 patients with essential hypertension who were given a regular sodium diet(12-15 g/day of NaCl) in the 1st & 3rd weeks and a sodium restricted diet(0-3 g/day) in the 2nd & 4th weeks. One of three antihypertensive drugs, 60 mg/day of nicardipine(Ca-antagonist), 120 mg/day of propranolol(β-blocker) or 150 mg/day of captopril(converting enzyme inhibitor) was administered in the 3rd & 4th weeks. Urinary sodium excretion was plotted on the ordinate as a function of mean arterial pressure before and after administration of the antihypertensive drugs.

The hypotensive effect of nicardipine, being independent of the amount of sodium intake, was based on the leftward shift of the renal function curve, probably due to the decrease in renal vascular resistance. The effects of propranolol and captopril, being augmented under sodium restriction, were based on the combination of the left-ward shift and the decrease in the slope. The decrease in the slope might be due in part to the inhibition of the renin-angiotensin system. Diuretics, the effect of which is suppressed under sodium restriction, may increase the slope of the renal function curve and potentiate the hypotensive effects of propranolol and captopril.